583-252-0 FWC DIV

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF:

MANFRED ASSMUS ET AL : GROUP ART UNIT: 1712

SERIAL NO. 08/813,950

FILED: MARCH 3, 1997 : EXAMINER: SELLERS

FOR: THERMOPLASTIC COATING AND BINDING AGENT FOR MEDICINAL FORMS

APPEAL BRIEF

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

This is an appeal from the final rejection of Claims 17-24.

Proposed Findings of Facts and conclusion of Law are included as Appendix II herewith. See Gechter v. Davidson, 43 USPQ2d 1030.

I. REAL PARTY IN INTEREST

The real party in interest is Roehm GMBH Chemische Fabrik, the assignment having been recorded on February 16, 1996 at Reel/Frame 7976/0151.

II. RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known to Applicants, Applicants' legal representative, or assignee, which will directly effect or be directly affected by or having a bearing on the Board's decision in the pending appeal.

III. STATUS OF THE CLAIMS

The appeal claims are Claims 17-24.

Claims 1, 3, 5, 7, 9, 11, 13 and 15, all of the other claims remaining in the case, stand withdrawn from consideration as not reading on the elected invention.

IV. STATUS OF THE RESPONSES FILED UNDER 37 C.F.R. §1.116

The responses under 37 C.F.R. §1.116 filed October 5, 1999 and June 21, 1999, accompanied by declarations under 37 C.F.R. §1.132, were entered and considered by the Examiner, as so stated by him in his Advisory Actions of June 29, 1999 and October 14, 1999.

V. THE APPEALED CLAIMS

A copy of the appealed claims is provided in Appendix I attached hereto.

VI. SUMMARY OF THE INVENTION

The invention relates to an oral or dermal medicinal composition containing a pharmaceutical active substance and a thermoplastic coating and binding agent prepared by a method of applying a thermoplastic coating and binding agent in a hot-melt liquid state at a temperature of 100-150°C to said oral or dermal medicinal composition, followed by cooling to solidify the thermoplastic coating and binding agent, wherein said thermoplastic coating and binding agent consists essentially of a non-homogeneous mixture of based on 100% by weight of A and B:

A) 5-95% of a thermoplastic acrylic plastic with a melting temperature above room temperature and below 200°C, a glass transition temperature below 120°C, and a melt

viscosity of 1,000 to 1,000,000 Pa-sec at the melting temperature; and

B) 95-5 wt.% of a flow improver, which, at room temperature, is not compatible with the thermoplastic acrylic plastic, has a melting temperature above room temperature but below 200°C, a weight average molecular weight under 20,000 d. and a melt viscosity below 100 Pa-sec at the melting temperature of the acrylic plastic.

Claim 17, the generic claim in the case, finds basis at page 1, lines 6-11, page 5, line 12 to page 6, line 2, and at page 16, lines 9 to 10 of the specification.

Claims 18-20 more particularly define component A, consistent with the disclosure at page 8, line 22 to page 9, line 2 of the specification.

Claims 21 to 24 more particularly define component B, consistent with the disclosure at page 13, line 6 to page 15, line 2 of the specification.

VII. THE ISSUE OF THIS APPEAL

The sole issue for adjudication by this appeal is obviousness, within the meaning of 35 U.S.C. §103(a), over DeHaan, Mueller (Canadian patent) and the European patent.

VIII. GROUPING OF THE CLAIMS

The claims are not urged to define separate and distinct inventions, they standing or falling together.

IX. ARGUMENTS IN TRAVERSAL OF THE REJECTION

As discussed at pages 1-3 of the specification, in addition to the classical method for the preparation of solid medicinal forms by the pressing of tablets and sheathing with a coating agent dissolved or dispersed in a liquid phase, the preparation or sheathing of

medicinal forms from the melt-liquid state of the coating and binding agent is gaining increasing importance as a particularly economical and reliable preparative method. This requires thermoplastic coating and binding agents, which must fulfill a number of special requirement:

they must fulfill the dissolution or release requirements needed for the use of the medicinal form;

they must be meltable, undecomposed, and be capable of mixing in the solid state by cooling;

they must produce a dry, nonsticky surface upon solidification from the melt;

they should not damage the contained or sheathed pharmaceutical active substance under the conditions of thermoplastic processing.

The thermoplastic coating and binding agents available at present time do not meet these requirements to a satisfactory extent. This is true, above all, for coating and binding agents on the basis of acrylic plastics, which are generally known under the tradename EUDRAGIT from Röhm GmbH, Darmstadt. They are characterized by special solubility and release characteristics, which cannot be dispensed with for the preparation of delayed action preparations. Thus, EUDRAGIT E contains basic amino groups, which ensure the solubility in gastric juice. EUDRAGIT RL and RS contain quaternary ammonium groups, which control the active substance release independent of the pH value of the surrounding aqueous medium.

The preparation of medicinal forms by extrusion using thermoplastic coating and binding agents based on acrylic plastics has already been described. If aqueous dispersion or moist mixtures of these coating and binding agents are used with such methods and a drying step is used, they do not accomplish the goal of the thermoplastic preparation of medicinal

forms of the invention.

Applicants discovery provides for a thermoplastic coating and binding agent which fulfills the above described requirements. Release characteristics are obtained thereby which correspond approximately to those of conventional film coating made of aqueous dispersions or organic solutions. The prerequisite for this as realized by Applicants' discovery is an improved flowing capacity of the melt, without a plasticizing effect which would lead to sticky surfaces.

This object is achieved by an oral or dermal medicinal composition containing a pharmaceutical active substance and a thermoplastic coating and binding agent prepared by a method of applying a thermoplastic coating and binding agent in a hot-melt liquid state at a temperature of 100-150°C to said oral or dermal medicinal composition, followed by cooling to solidify the thermoplastic coating and binding agent, wherein said thermoplastic coating and binding agent consists essentially of a non-homogeneous mixture of based on 100% by weight of A and B:

A) 5-95% of a thermoplastic acrylic plastic with a melting temperature above room temperature and below 200°C, a glass transition temperature below 120°C, and a melt viscosity of 1,000 to 1,000,000 Pa-sec at the melting temperature; and

B) 95-5 wt.% of a flow improver, which, at room temperature, is not compatible with the thermoplastic acrylic plastic, has a melting temperature above room temperature but below 200°C, a weight average molecular weight under 20,000 d. and a melt viscosity below 100 Pa-sec at the melting temperature of the acrylic plastic.

It is the Examiner's position that it assertedly would be obvious to conduct the extrusions of the DeHaan and European patent within the temperature range of Mueller in order to facilitate the extrusion.

It is submitted that this is not a viable position, for the following reasons.

a) No *prima facie* case is made out by the teachings of the references, they also being improperly combined.

Thus, in DeHaan, no hot-melt application clearly is disclosed. As so shown by DeHaan in its Example 1 referred to be the Examiner, the restraining phase was obtained from a solution of the components in chloroform, and the housing phase was obtained from a powder mixture heated to 90°C until granuable, the mixture of the restraining phase and housing phase then being compacted. Such clearly does not involve a hot-melt extrusion and specifically at a temperature of 100-150°C, as claimed. Note that the restraining phase is obtained from a solution of "Eudragit" in chloroform, chloroform having a boiling point of 61°C heating to only 90°C is disclosed for the preparation of the housing phase, and no heat is applied during compaction of the restraining phase and housing phase mixture. It is thus readily apparent that DeHaan is not relevant to the claimed invention.

Mueller, discussed at page 3 of the specification with regard to its equivalent German Patent 4,138,513, discloses:

A solid depot drug form product by melt extrusion at from 50 to 200°C and continuous shaping of a mixture of from 0.1 to 70% by weight, based on the finished depot form, of a pharmaceutical active ingredient with a polymer melt of the following composition:

a) a least 6% by weight, based on the complete depot form, of at least one water-insoluble poly(meth)acrylate with a glass transition temperature Tg in the rang of from -60 to 180°C,

b) a water-soluble hydroxyalkylcellulose or hydroxy-alkymethylcellulose with 2 or 3 carbons in the hydroxyalkyl, or an N-vinylpyrrolidone polymer with from

0 to 50% by weight of vinyl acetate or a mixture of the two

in the ratio a):b) = 5:95 to 95:5, and

c) 0-30% by weight, based on the finished depot form, of one or more conventional pharmaceutical auxiliaries.

In other words, it discloses a composition of a homogenous mixture of a) and b), optionally also containing component c). Such a composition clearly is distinctly different from the composition used in the preparation of the claimed medicinal composition consisting essentially of a non-homogenous mixture of A and B.

In Mueller, essential to its - invention is that its pharmaceutical sustained-release composition contain its defined component b) in addition to defined components a) and c). The presence of component b) essential in the invention of Mueller, however, is precluded by the "consisting essentially of" language of the claims. Note the Examiner's acknowledgment to this effect with regard to his withdrawal of the rejection of the claims over Mueller at page 2 of the Official Action Of July 27, 1998. Consequently, even if component c) of the reference assertedly reads on claimed component B, the claimed invention is not made obvious thereby. Rather, Mueller quite evidently teaches away from Applicants' discovery. Moreover, and in any event, the claimed limitation with regard to incompatibility also is not so disclosed by Mueller, nor obvious therefrom. Additionally, hydroxyalkylcellulose usually have molecular weights much greater than 20,000 d. as compared to claimed component B) having an average molecular weight of under 20,000 d. so claimed.

Similarly, in the European patent two lipid excipients, one of which can dissolve or gel component A while the other acts as a lubricant, or, alternatively, a single lipid excipient having both of these functions is used in the extrusion of a medicinal material. Here again the

reference teaches away from the claimed invention in requiring that the composition be a homogenous mixture, i.e., containing a lipid excipient which can dissolve the gel component A. Such is contrary to the express requirement of the present claims wherein the mixture of A and B is specifically defined as consisting essentially of a non-homogeneous mixture of A and B.

The defined incompatibility, i.e., non-homogenous mixture, has the effect that in the solidified melt, components A and B are present as separate phases, and flow improver B is not present dissolved in polymer phase A as a plasticizer. Such provides for an improved flowing capacity of the melt, without a plasticizing effect which would lead to sticky surfaces. Such clearly is not obvious from the references.

In the European patent the excipients are selected in such a way that they exert a dissolving or gelling effect and a lubricating effect on the polymer. By using such excipients a homogeneous mixture is formed which is compatible even after solidification due to the dissolving or gelling effect of the excipients. A solidified composition obtained from the melt thus remains soft and sticky on its surface, not being suitable as a surface on a medicinal composition. This is not the case in the claimed invention where the defined components A and B are heated to a temperature of 100-150°C and are so selected that their combination provides for an incompatible, nonhomogeneous mixture upon solidification. This clearly is against the express requirement of the reference.

Specifically, when a nonhomogeneous mixture would be obtained by using an excipient selected from the classes of materials disclosed by the European patent, such excipient would not be useful for attaining patentee's objective. Note that homogeneity depends not only on the requisite selection of a particular excipient, but also in combining

such selected excipient with a particular polymer and at a specified temperature. Thus, while in Example 17 of the European patent referred to by the Examiner a polymer within the scope of the claims is present, nevertheless, only a specific excipient is illustrated as being combinable therewith, such specific excipient, however, providing for a homogeneous mixture wherein the excipient has a plasticizing effect to dissolve or gel the polymer which does not separate upon cooling due to the dissolving or gelling effect and not having been heated to the requisite temperature. In the claimed invention, on the other hand, contrariwise the selected combination of components and heating must be such so as to obtain an incompatible, nonhomogeneous mixture of the components upon cooling. Such selection and condition clearly are contraindicated and not inherent in the European patent, it manifestly teaching away therefrom.

It is thus readily apparent that the references, even in combination, do not make obvious the claimed invention. It is not apparent why one skilled in the art would have any motivation or incentive to use the extrusion temperature of 65°C disclosed by the European patent in the system of DeHaan and/or Mueller. They, for reasons as pointed out and discussed above, relate to significantly and materially different systems. In fact, no hot-melt extrusion is disclosed by DeHaan. Also, the "consisting essentially" language of the claims precludes the presence in Mueller of its component b) materially affecting the basic and novel characteristics of its composition. The references thus clearly are not properly combinable. In re Fine, 5 USPQ 2nd 1596.

b) The showing in the Declarations under 37 C.F.R. §1.132 rebut any possible presumption of obviousness of the claimed invention.

In the interview with the Examiner, Mr. Sellers, on March 16, 1999, the Examiner stated:

Evidence addressing the claimed mixing temperature range of from 100-150°C over the closest prior art temperature of 65°C in Exs. 1 and 17 of European patent would be considered for those species of flow improvers tested wherein the types and amounts of acrylic A) and flow improver B) are held constant and mixing temperatures of 65°C, 100°C and 150°C are employed.

A Declaration Under 37 C.F.R. § 1.132 believed to be consistent with the Examiner's requirement for demonstrating unobviousness of the claimed invention thus was filed on June 21, 1999. A copy of this Declaration is attached for the Board's convenience. In the Advisory Action of June 29, 1999, however, the Examiner considered the showing in this Declaration to be inconclusive inasmuch as there is no comparison involving melts at the lower, midrange and upper limits of the claimed melt temperature range of 100 to 100°C to compare with the results at the prior art temperature of 65°'C. Further, the results are based on visual observations which are a function of the observer and cannot be verified in the absence of an empirical basis for the determination of melt appearance, such as microphotographs. Also, the showings are not commensurate in scope with the claims because the testing of a single type of flow improver does not confer patentability to the class of flow improvers as claimed.

A Supplemental Declaration Under 37 C.F.R. § 1. 132 thus was filed on October 5, 1999, remedying the inadequacies asserted by the Examiner. Specifically, the Supplemental Declaration, also attached for the Board's convenience, factually establishes unexpected results with representative additional flow improvers of the claimed class at the claimed mixing temperature range, as compared to the 65°C mixing temperature of the European patent, the acknowledged closest prior art. The Examples in the Declaration are with the same components and concentrations, the only difference being mixing temperatures.

In the Advisory Action of October 14, 1999, in response thereto, the Examiner still adhered to his rejection, stating:

> The evidence presented in the declaration filed October 5, 1999 is unpersuasive. The microphotographs for stearyl alcohol and 50% by weight of glycerol monostearate show differences in homogeneity between hot-melt application at 65°C (representative of the closest prior art) vs. 100°C and 150°C (reflective of the claimed range) if interpreted by the presence of a thick dark outline. However, no distinction in homogeneity is seen when comparing stearic acid, polyethylene glycol, and 80% by weight of glycerol monostearate at 65°C vs. 100°C.
>
> Since it is apparent that homogeneity is a function of the type of flow improver and the amount of given species of flow improver, the evidence is not commensurate in scope with the claims regarding a representative sampling of the other untested species of flow improvers such as the chemically distinct sugar or ester thereof, a triglyceride and wax. Furthermore, the showings are not commensurate in scope with the claimed wide proportion of flow improver of from 5-95% by weight via the testing at only 50% and 80% by weight of glycerol monostearate.
>
> The data from the declaration filed June 21, 1999 wherein from 20-80% by weight of glycerol monostearate is tested is deficient due to the lack of microphotographic corroboration of the mere visual observations of the homogeneity. Such a range does not confirm the criticality of a flow improver level of as low as 5% by weight and as high as 95% by weight which, according to the second declaration, exhibits less homogeneity as the concentration increases (Compare 50% by weight of glycerol monostearate vs. 80% by weight thereof).

As so acknowledged by the Examiner, unexpected results, in fact, have been demonstrated for the claimed invention, but assertedly, not for the scope as claimed. It is submitted that this is not a viable position.

Specifically, while a comparison is not made with all of the possible flow improves encompassed by generic Claims 17-19, nor of all of the embodiments embraced by Claims 21-24, nevertheless, comparisons palpably are made with representative members and at

representative proportions thereof, at the closest prior art temperature, i.e., 65°C, and demonstrating unexpected improvements.

It is to be noted and pointed out that possible embodiments not resulting in unexpected results are not within the scope of the claims which specifically require that components A and B are not compatible with each other and that they form a hot-melt liquid at a temperature of 100-150°C. Also, of course, the flow improvers shown manifestly are representative of the defined genus B, even though all possible embodiments thereof are not so shown in the Declarations. The same is true for the temperatures and amounts of components shown which manifestly are representative.

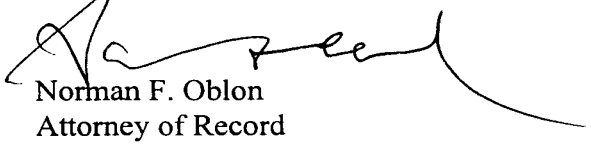
Further, the Examiner criticism of the interpretation of the microphotographs contrary to Declarants conclusion clearly is not well taken. Full credence and weight must be given to Declarants' statements and conclusion, he being one skilled in this art. Note In re Soni, 34 USPQ 2nd 1684.

X. RELIEF REQUESTED

Reversal of the Examiner's rejection of the claims under 35 U.S.C. §103 is requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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APPENDIX I

1. The Appeal Claims read as follows:

17. An oral or dermal medicinal composition containing a pharmaceutical active substance and a thermoplastic coating and binding agent prepared by a method of applying a thermoplastic coating and binding agent in a hot-melt liquid state at a temperature of 100-150°C to said oral or dermal medicinal composition, followed by cooling to solidify the thermoplastic coating and binding agent, wherein said thermoplastic coating and binding agent consists ~~essentially~~ of a non-homogeneous mixture of based on 100% by weight of A and B:

A) 5-95% of a thermoplastic acrylic plastic with a melting temperature above room temperature and below 200°C, a glass transition temperature below 120°C, and a melt viscosity of 1,000 to 1,000,000 Pa-sec at the melting temperature; and

B) 95-5 wt.% of a flow improver, which, at room temperature, is not compatible with the thermoplastic acrylic plastic, has a melting temperature above room temperature but below 200°C, a weight average molecular weight under 20,000 d. and a melt viscosity below 100 Pa-sec at the melting temperature of the acrylic plastic.

18. An oral or dermal medicinal composition containing a pharmaceutical active substance and a thermoplastic coating and binding agent prepared by the method as defined in Claim 17, wherein the thermoplastic acrylic plastic A is a copolymer of esters of acrylic and/or methacrylic acid.

19. An oral or dermal medicinal composition containing a pharmaceutical active substance and a thermoplastic coating and binding agent prepared by the method as defined in Claim 17, wherein the thermoplastic acrylic plastic A is a copolymer of alkyl esters of acrylic

and/or methacrylic acid and functional comonomers with coherently bound cationic groups.

20. An oral or dermal medicinal composition containing a pharmaceutical active substance and a thermoplastic coating and binding agent prepared by the method as defined in Claim 17, wherein the thermoplastic acrylic plastic A is a copolymer of 5 to 99 wt% alkyl esters of acrylic and/or methacrylic acid and 95 to 1 wt% aminoalkyl esters of aminoalkylamides of acrylic and/or methacrylic acid or their salts or quaternary ammonium compounds thereof.

21. An oral or dermal medicinal composition containing a pharmaceutical active substance and a thermoplastic coating and binding agent prepared by the method as defined in Claim 17, wherein flow improver B is a fatty alcohol, a fatty acid, an ester of a fatty alcohol and a fatty acid, a sugar, an ester thereof, a fatty acid mono-, di- or triglyceride, a polyethylene glycol, a fatty acid ester or fatty alcohol ether thereof, a wax, or mixtures of any of the above.

22. An oral or dermal medicinal composition containing a pharmaceutical active substance and a thermoplastic coating and binding agent prepared by the method as defined in Claim 18, wherein flow improver B is a fatty alcohol, a fatty acid, an ester of a fatty alcohol and a fatty acid, a sugar, an ester thereof, a fatty acid mono-, di- or triglyceride, a polyethylene glycol, a fatty acid ester or fatty alcohol ether thereof, a wax, or mixtures of any of the above.

23. An oral or dermal medicinal composition containing a pharmaceutical active substance and a thermoplastic coating and binding agent prepared by the method as defined in Claim 19, wherein flow improver B is a fatty alcohol, a fatty acid, an ester of a fatty alcohol and a fatty acid, a sugar, an ester thereof, a fatty acid mono-, di- or triglyceride, a polyethylene glycol, a fatty acid ester or fatty alcohol ether thereof, a wax, or mixtures of any of the above.

24. An oral or dermal medicinal composition containing a pharmaceutical active substance and a thermoplastic coating and binding agent prepared by the method as defined in

Claim 20, wherein flow improver B is a fatty alcohol, a fatty acid, an ester of a fatty alcohol and a fatty acid, a sugar, an ester thereof, a fatty acid mono-, di- or triglyceride, a polyethylene glycol, a fatty acid ester or fatty alcohol ether thereof, a wax, or mixtures of any of the above.

APPENDIX II

A. Finding of Facts

1. An oral or dermal medicinal composition containing a pharmaceutical active substance and a thermoplastic coating and binding agent prepared by a method as defined by the claims is not obvious from the references relied upon by the Examiner.

2. No hot-melt application is disclosed by DeHaan, it not being related to the claimed invention.

3. Mueller is directed to a significantly and materially different composition, not consisting essentially of a mixture of defined components A and B not compatible at room temperature, the "consisting essentially of" language of the claims also precluding the presence of its essential components c).

4. The composition of European patent is not comparable to the one as claimed, its plasticized composition remaining soft and sticking on it surface, such surface not being suitable on a medicinal composition.

5. The references are improperly combined, they relating to significantly and materially different compositions with different effects and characteristics.

6. No reason is present which would motivate one skilled in the art, nor would he have any incentive, to combine the diverse teachings of the references so as to arrive at the claimed invention.

7. Any possible *prima facie* case of obviousness made out even by combining the references stands rebutted by the comparative evidence in the case.

8. The Declarations under 37 C.F.R. §1.132, by representative examples, establish unobvious and unexpected results due to the claimed limitations, thereby rebutting any *prima*

facie case of obviousness conceivably made out by the art.

B. Conclusion of Law

1. Several basic factual inquiries must be made in order to determine obviousness or non-obviousness of claims of a patent application under 35 U.S.C. § 103. These factual inquiries are set forth in Graham v. John Deere Co., 383 U.S. 1,17,148 USPQ 459,467 (1966):

> Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness of the subject matter is determined.

The specific factual inquiries set forth in Graham have no been considered or properly applied by the Examiner in formulating the rejection of the subject claims. Particularly, the scope and content of the prior art and the level of ordinary skill in the pertinent art were not properly determined, demonstrated and applied to the claimed invention. In the present case, proper consideration of the factual inquiries demonstrates the non-obviousness of the claimed invention.

2. The claimed subject matter would not have been obvious over the prior art.

3. The claimed invention is patentable under 35 U.S.C. § 103.